

WHAT IS CLAIMED IS:

1. A method of treating a bone disease comprising:  
administering to a mammal in need of said treatment a therapeutically effective amount of a  
compound that lowers leptin level in blood serum, wherein the bone disease is characterized  
5 by a decreased bone mass relative to that of corresponding non-diseased bone.

2. The method of claim 1, wherein said leptin level is lowered by lowering leptin  
synthesis.

10 3. The method of claim 2, wherein said compound is an antisense, ribozyme or  
triple helix sequence of a leptin-encoding polynucleotide.

15 4. The method of claim 1, wherein said bone disease is selected from the group  
consisting of osteoporosis, osteopenia, and Paget's disease.

20 5. A method of treating a bone disease comprising:  
administering to a mammal in need of said treatment a therapeutically effective amount of a  
compound that lowers leptin level in cerebrospinal fluid, wherein the bone disease is  
characterized by a decreased bone mass relative to that of corresponding non-diseased bone.

6. The method of claim 5, wherein said compound binds leptin in blood.

25 7. The method of claim 6, wherein said bone disease is selected from the group  
consisting of osteoporosis, osteopenia, and Paget's disease.

30 8. A method of treating a bone disease comprising:  
administering to a mammal in need of said treatment a therapeutically effective amount of a  
compound, wherein the bone disease is characterized by a decreased bone mass relative to  
that of corresponding non-diseased bone, and wherein the compound is selected from the  
group consisting of: an antibody which specifically binds leptin, a soluble leptin receptor

polypeptide, an inter-alpha-trypsin inhibitor heavy chain related protein and an alpha 2-macroglobulin protein.

9. The method of claim 8, wherein said antibody is a monoclonal antibody.

10. The method of claim 8, wherein said antibody is a human or chimeric antibody.

11. The method of claim 10, wherein said antibody is a humanized antibody.

12. The method of claim 8, wherein said bone disease is selected from the group consisting of osteoporosis, osteopenia, and Paget's disease.

13. A method of treating a bone disease comprising:  
administering to a mammal in need of said treatment a therapeutically effective amount of a compound that lowers the level of phosphorylated Stat3 polypeptide, wherein the bone disease is characterized by a decreased bone mass relative to that of corresponding non-diseased bone.

14. The method of claim 13, wherein said compound is a leptin receptor antagonist.

15. The method of claim 14, wherein said leptin receptor antagonist is an acetylphenol.

16. The method of claim 14, wherein said leptin receptor antagonist is an antibody selected from the group consisting of an antibody which specifically binds leptin and an antibody which specifically binds leptin receptor.

17. The method of claim 13, wherein said bone disease is selected from the group consisting of osteoporosis, osteopenia, and Paget's disease.

18. The method of claim 1, 5 or 13 further comprising administering to the mammal a therapeutically effective amount of a selective estrogen receptor modulator.

5 19. The method of claim 18, wherein said selective estrogen receptor modulator is estradiol.

20. A method of preventing a bone disease comprising:  
administering to a mammal at risk for the bone disease a compound that lowers leptin level in  
10 blood serum, at a concentration sufficient to prevent the bone disease, wherein the bone disease is characterized by a decreased bone mass relative to that of corresponding non-diseased bone.

21. The method of claim 20, wherein said leptin level is lowered by lowering  
15 leptin synthesis.

22. The method of claim 21, wherein said compound is an antisense, ribozyme or triple helix sequence of a leptin-encoding polynucleotide.

20 23. The method of claim 20, wherein said bone disease is selected from the group consisting of osteoporosis, osteopenia, and Paget's disease.

24. A method of preventing a bone disease comprising:  
administering to a mammal at risk for the bone disease a compound that lowers leptin level in  
25 cerebrospinal fluid, at a concentration sufficient to prevent the bone disease, wherein the bone disease is characterized by a decreased bone mass relative to that of corresponding non-diseased bone.

25. The method of claim 24, wherein said compound binds leptin in blood.  
30

26. The method of claim 24, wherein said bone disease is selected from the group consisting of osteoporosis, osteopenia, and Paget's disease.

27. A method of preventing a bone disease comprising:  
5 administering to a mammal at risk for the bone disease a compound at a concentration sufficient to prevent the bone disease, wherein the bone disease is characterized by a decreased bone mass relative to that of corresponding non-diseased bone, and wherein the compound is selected from the group consisting of: an antibody which specifically binds leptin, a soluble leptin receptor polypeptide, an inter-alpha-trypsin inhibitor heavy chain  
10 related protein and an alpha 2-macroglobulin protein.

28. The method of claim 27, wherein said antibody is a monoclonal antibody.

29. The method of claim 27, wherein said antibody is a human or chimeric  
15 antibody.

30. The method of claim 29, wherein said antibody is a humanized antibody.

31. The method of claim 27, wherein said bone disease is selected from the group  
20 consisting of osteoporosis, osteopenia, and Paget's disease.

32. A method of preventing a bone disease comprising:  
administering to a mammal at risk for the bone disease a compound that lowers the level of phosphorylated Stat3 polypeptide, at a concentration sufficient to prevent the bone disease,  
25 wherein the bone disease is characterized by a decreased bone mass relative to that of corresponding non-diseased bone.

33. The method of claim 32, wherein said compound is a leptin receptor  
30 antagonist.

34. The method of claim 33, wherein said leptin receptor antagonist is an acetylphenol.

35. The method of claim 33, wherein said leptin receptor antagonist is selected from the group consisting of an antibody which specifically bind leptin and an antibody which specifically binds leptin receptor.

36. The method of claim 32, wherein said bone disease is selected from the group consisting of osteoporosis, osteopenia, and Paget's disease.

37. A method of diagnosing a bone disease in a mammal comprising:  
(a) measuring leptin levels in blood serum of a mammal; and  
(b) comparing the level measured in (a) to the leptin level in control blood serum,  
so that if the level obtained in (a) is higher than that of the control, the mammal is diagnosed as exhibiting the bone disease, wherein the bone disease is characterized by a decreased bone mass relative to that of corresponding non-diseased bone.

38. The method of claim 37, wherein said mammal is a human.

39. The method of claim 37, wherein said bone disease is selected from the group consisting of osteoporosis, osteopenia, and Paget's disease.

40. A method of diagnosing a bone disease in a mammal comprising:  
(a) measuring leptin levels in cerebrospinal fluid of a mammal; and  
(b) comparing the level measured in (a) to the leptin level in control cerebrospinal fluid,  
so that if the level obtained in (a) is higher than that of the control, the mammal is diagnosed as exhibiting the bone disease, wherein the bone disease is characterized by a decreased bone mass relative to that of corresponding non-diseased bone.

41. The method of claim 40, wherein said mammal is a human.

42. The method of claim 40, wherein said bone disease is selected from the group consisting of osteoporosis, osteopenia, and Paget's disease.

5

43. A method for identifying a compound to be tested for an ability to modulate bone mass in a mammal, comprising:

- (a) contacting a test compound with a polypeptide; and
- (b) determining whether the test compound binds the polypeptide, so that if the test compound binds the polypeptide, then a compound to be tested for an ability to modulate bone mass is identified,

10

wherein the polypeptide is selected from the group consisting of a leptin polypeptide and a leptin receptor polypeptide.

15

44. The method of claim 43, wherein said polypeptide is a human polypeptide

45. The method of claim 43, wherein said ability to modulate bone mass is the ability to increase bone mass.

20

46. The method of claim 43, wherein said ability to modulate bone mass is the ability to decrease bone mass.

47. A method for identifying a compound that modulates bone mass in a mammal, comprising:

25

- (a) contacting test compounds with a polypeptide;
- (b) identifying a test compound that binds the polypeptide; and
- (c) administering the test compound in (b) to a non-human mammal, and determining whether the test compound modulates bone mass in the mammal relative to that of a corresponding bone in an untreated control non-human mammal,

30

wherein the polypeptide is selected from the group consisting of a leptin polypeptide and a leptin receptor polypeptide, so that if the test compound modulates bone mass, then a compound that modulates bone mass in a mammal is identified.

5           48.     The method of claim 47, wherein said polypeptide is a human polypeptide.

          49.     The method of claim 47, wherein said ability to modulate bone mass is the ability to increase bone mass.

10

          50.     The method of claim 47, wherein said ability to modulate bone mass is the ability to decrease bone mass.

          51.     A method for identifying a compound to be tested for an ability to modulate bone mass in a mammal, comprising:

15

          (a)     contacting a test compound with a leptin polypeptide and a leptin receptor polypeptide for a time sufficient to form leptin/leptin receptor complexes; and

          (b)     measuring leptin/leptin receptor complex level,  
so that if the level measured differs from that measured in the absence of the test compound,  
then a compound to be tested for an ability to modulate bone mass is identified.

20

          52.     The method of claim 51, wherein said leptin polypeptide is a human polypeptide.

25           53.     The method of claim 51, wherein said leptin receptor polypeptide is a human polypeptide.

          54.     The method of claim 51, wherein said ability to modulate bone mass is the ability to increase bone mass.

30

55. The method of claim 51, wherein said ability to modulate bone mass is the ability to decrease bone mass.

56. A method for identifying a compound to be tested for an ability to decrease bone mass in a mammal, comprising:

- (a) contacting a test compound with a cell which expresses a functional leptin receptor; and
  - (b) determining whether the test compound activates the leptin receptor,
- wherein if the compound activates the leptin receptor a compound to be tested for an ability to decrease bone mass in a mammal is identified.

57. A method for identifying a compound that decreases bone mass in a mammal, comprising:

- (a) contacting a test compound with a cell that expresses a functional leptin receptor, and determining whether the test compound activates the leptin receptor;
- (b) administering a test compound identified in (a) as activating the leptin receptor to a non-human animal, and determining whether the test compound decreases bone mass of the animal relative to that of a corresponding bone of a control non-human animal,

so that if the test compound decreases bone mass, then a compound that decreases bone mass in a mammal is identified.

58. A method for identifying a compound to be tested for an ability to increase bone mass in a mammal, comprising:

- (a) contacting a leptin polypeptide and a test compound with a cell that expresses a functional leptin receptor; and
- (b) determining whether the test compound lowers activation of the leptin receptor relative to that observed in the absence of the test compound;

wherein a test compounds that lowers activation of the leptin receptor is identified as a compound to be tested for an ability to increase bone mass in a mammal.



59. A method for identifying a compound that increases bone mass in a mammal, comprising:

- 5 (a) contacting a leptin polypeptide and a test compound with a cell that expresses a functional leptin receptor, and determining whether the test compound decreases activation of the leptin receptor;
- (b) administering a test compound identified in (a) as decreasing leptin receptor to a non-human animal, and determining whether the test compound increases bone mass of the animal relative to that of a corresponding bone of a control non-human animal,

10 so that if the test compound increases bone mass, then a compound that increases bone mass in a mammal is identified.

60. The method of claim 56, 57, 58 or 59 in which activation of the leptin receptor is determined by measuring levels of phosphorylated Stat3 polypeptide.